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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/125,460	08/19/98	WALDMANN	H 1283-36

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EXAMINER	
GAMBEL, P	
ART UNIT	PAPER NUMBER
1644	15

DATE MAILED: 09/05/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/125460	WALDMANN
Examiner	**Group Art Unit**
GAMBEL	1644

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☑ Responsive to communication(s) filed on 11/9/99; 8/2/00.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disp sition of Claims

☑ Claim(s) 1-22, 24 is/are pending in the application.

Of the above claim(s) 18-22, 24 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☑ Claim(s) 1-17, 22 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☑ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☑ The proposed drawing correction, filed on _____ is ☑ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____.

Attachm nt(s)

☑ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☑ Notice of Reference(s) Cited, PTO-892

☑ Notice of Draftsperson's Patent Drawing R view, PTO-948

☐ Interview Summary, PTO-413

☐ Notice of Informal Patent Application, PTO-152

☐ Other _____

Office Action Summary

DETAILED ACTION

1. Claims 23 has been canceled previously.
Claims 1-22 and 24 are pending.

2. Applicant's election with traverse of Group I (claims 1-17 and 22) in Paper No. 7, filed 11/9/00, is acknowledged. The traversal is on the ground(s) that Groups II/III contain elements of Group I and that there would be no serious burden on the examiner. This is not found persuasive because of the reasons of record. This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. and therefore do not set forth a technical feature which is a contribution over the prior art. Also, in the instant case, the product as claimed can be used in a materially different process such as affinity purification procedures or detection assays. Further, in the instant case, the antibodies can be made by a variety of recombinant and biochemical procedures.

The requirement is still deemed proper and is therefore made FINAL.

Claims 18-21 and 24 are withdrawn from further consideration by the examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention.

3. The instant application is in compliance with the sequence rules for patent applications containing nucleotide sequence and/or amino acid sequence disclosures.

4. This application does not contain an Abstract of the disclosure as required by 37 CAR 1.72(b). An abstract on a separate sheet is required.

5. Applicant should amend the first line of the specification to update the status (and relationship) of the priority documents.

6. Formal drawings, filed 5/18/98, comply with 37 CAR 1.84.
Please see the enclosed form PTO-948.

7. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected.

Applicant is required to identify the nucleotide and amino acid sequences in the specification with SEQ. ID NOS.

Trademarks (e.g. CAMPATH-1) should be capitalized or accompanied by the ™ or ® symbol wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Appropriate corrections are required

8. The following is a quotation of the first paragraph of 35 U.S.C. § 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. claims 1-17 and 22 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention

Applicant has not disclosed how to make and use modified antibodies with reduced affinity for cell surface antigen which induce immunological tolerant to the therapeutic antibody. There is insufficient objective evidence to support the ability to make and use such modified antibodies to accomplish the claimed therapeutic endpoint of tolerance, encompassed by the claimed invention.

In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Since the therapeutic indices of biopharmaceutical drugs and particularly tolerance induction can be species- and model-dependent, it is not clear that reliance on the limited in vivo experimental models with modified CAMPATH-1 antibody in a transgenic mouse expressing CD52 accurately reflects the relative efficacy of the claimed products to induce tolerance commensurate in scope with the claimed invention, encompassing a variety of therapeutic antibodies and divergent structures as well as in a variety of hosts, particularly humans.

Although modified antibodies may be able to induce some specific immunosuppression with respect to a particular antibody in a particular transgenic animal model; it is not clear that a state of immunological tolerance can be achieved over the broad range of diverse therapeutic antibodies in humans. More importantly, it is not clear that the skilled artisan would extrapolate the ability to induce immunological tolerance from this limited information on certain particular modifications of one particular antibody in one particular experimental animal model to the breadth of modified therapeutic antibodies encompassed by the claimed invention. It is not clear that the instant murine experimental transgenic model provides the complexity of immunological barriers associated with generating immunological tolerance encompassed by the claimed invention. One of the problems with murine systems is the ease with rejection can be suppressed.

Long term immunological unresponsiveness or tolerance induction in humans has been one of the Holy Grails of therapeutic immunology. With respect to the unpredictability of tolerance induction in humans, the following is noted from Auchincloss (in Transplantation Immunology, Bach and Auchincloss, Eds.,. Wiley-Liss, New York, 1995; see Chapter 11, pages 211-218, particularly pages 211 and Conclusion). Tolerance is the long-lasting nonreactivity of the immune system to a specific set of antigens, maintained without on-going immunosuppression. Many different strategies have been developed to achieve transplantation tolerance some have which led to indefinite graft survival in rodents, none of these strategies have yet been applied to human patients in a way that allows reliable withdrawal or exogenous immunosuppression. While tolerance inducing strategies that have worked well in rodents, such strategies have been much less successful even when tested in nonhuman primates and other large animals. Also, the Conclusion on page 217 indicates that: Although more than a dozen different techniques to induce tolerance in rodents are now available, the fact remains that none of them has been used successfully in the clinic. Inducing transplantation tolerance in human must therefore be very hard to do. And that reading of this chapter should make one wary of simple solutions to this complex problems.

In view of the lack of predictability of the art to which the invention pertains the lack of established clinical protocols for effective tolerance-induction therapies, undue experimentation would be required to practice the claimed therapeutic in vivo methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed inventions and absent working examples providing evidence which is reasonably predictive that the claimed products are effective for inducing antigen-specific tolerance.

Applicant is invited to consider alternative recitations that focus more on the structure of the claimed modified antibodies rather than their intended use currently recited of inducing tolerance. The amendments must be supported by the specification so as not to add any new matter.

10. claims 1-17 and 22 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention

Applicant has not provided direction and guidance as how to make and to use modified versions of therapeutic antibodies and fragments thereof which results in a reduced affinity for antigen from the pertinent therapeutic antibody.

The instant claims are drawn to modified antibodies including independent claim 1 which recites that the antibody is not a mixed molecule antibody having an H or L chain of the therapeutic antibody paired with and L or H chain of an unrelated antibody.

As pointed out below in the rejection under 35 USC 112, second paragraph; this recitation is inconsistent with the dependent claims and the disclosure of the specification.

It is noted that fragments of the modified antibodies do not recite functional language (e.g. antigen binding fragments); therefore not all fragments, particularly the non-antigen binding fragments which retain functional activity (e.g. Fc fragments) would not be expected to have the intended functional activity, yet such fragments would have reduced affinity for cell surface antigens.

Given the absence of structural elements in the claims (e.g. amino acid sequences, deposited antibodies) or disclosure of structural elements in the specification as filed; there is insufficient guidance and direction as to how to make and use the claimed modified antibodies encompassing modifications, both substantially the same sequences as well as alterations and substitutions. Such modified antibodies and their therapeutic antibody counterparts encompass structural elements which are not readily apparent in the instant application as filed. The instant specification indicates that it is desirable to start with a solved crystal structure, preferably one that is co-crystallized with antigen so that the key contact residues be identified and substituted (see page 14, paragraph 2). Here, it is noted that alternative means to achieving said modifications including good molecular models, CDR swapping experiments , alanine scanning mutagenesis and genetic techniques such as phage display.

However, minor structural differences among structurally related compounds or compositions can result in substantially different biological activities. The claims not only encompass modified antibodies from ill-defined therapeutic antibodies and a myriad of cell surface specificities including a number of modifications including alterations, substitutions and substantially the same sequences involving nucleic acids and fragments thereof. For example, the claimed substitutions encompass single or double amino acid substitutions without providing clear guidance as to exactly where said substitutions would be made and how the skilled artisan would predict which therapeutic antibody may be changed accordingly. In the absence of sufficient information as to the structure-function relationship of the antibody-antigen interactions; it would require undue experimentation to practice the invention in a manner commensurate in scope with the claims, that is, to predict which of the innumerable modifications encompassed by the claimed invention would reasonably be expected to provide antibodies capable of inducing immunological tolerance to therapeutic antibodies.

Applicant has not provided sufficient biochemical information (e.g. amino acid sequence) nor has provide sufficient deposit information to enable the claimed therapeutic antibodies and, in turn, to enable the claimed modified versions of said therapeutic antibodies.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. Without sufficient guidance, the changes which can be made in the structure of therapeutic antibodies such that the modified versions of therapeutic antibodies and fragments thereof results in a reduced affinity for antigen from the pertinent therapeutic antibody and, in turn, provides or maintains sufficient activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue

11. Claims 1-17 and 22 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

It is noted that this is a written description rejection rather than an enablement rejection under 35 U.S.C. 112, first paragraph.

The instant claims are drawn to modified antibodies including independent claim 1 which recites that the antibody is not a mixed molecule antibody having an H or L chain of the therapeutic antibody paired with and L or H chain of an unrelated antibody. Given the absence of structural elements in the claims (e.g. amino acid sequences, deposited antibodies); there is insufficient guidance and direction as to the written description of these modified antibodies encompassing modifications, both substantially the same sequences as well as alterations and substitutions. Such modified antibodies and their therapeutic antibody counterparts encompass structural elements such as sequences which do not meet the written description provision of 35 USC 112, first paragraph.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

The skilled artisan cannot envision the detailed chemical structure of the encompassed modified antibodies or their therapeutic antibody counterparts and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.
Thus, the specification fails to describe these DNA sequences. The Court further elaborated that generic statements are not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. Finally, the Court indicated that while applicants are not required to disclose every species encompassed within a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, defined by nucleotide sequence, falling within the scope of the genus, See The Regents of the University of California v. Eli Lilly and Company, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Therefore, there is insufficient written description for the claims modified antibodies under the written description provision of 35 USC 112, first paragraph.

12. Claim 10: It is apparent that the CAMPATH-1 antibody is required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 USC 112, first paragraph, may be satisfied by a deposit of the cell line / hybridoma which produces this antibody. See 37 CAR 1.801-1.809.

In addition to the conditions under the Budapest Treaty, applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If the original deposit is made after the effective filing date of an application for patent, the applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified. See MPEP 1.804(b).

13. Claims 1-17 and 22 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1-17 and 22 are indefinite in that the characteristics of the modified version of a therapeutic antibody and fragments thereof are ambiguous and unclear.

For example, independent claim 1 recites that the antibody is not a mixed molecule antibody having an H or L chain of the therapeutic antibody paired with and L or H chain of an unrelated antibody.

However the dependent claims recite and the specification discloses that the claims modified antibodies encompass humanized as well as chimeric antibodies. Therefore, the claims encompass recombinant antibodies comprising unrelated antibodies.

Also, given the absence of structural elements in the claims (e.g. amino acid sequences, deposited antibodies); the metes and bounds or defining characteristics of the claimed modified antibody versions encompassing modifications encompass both substantially the same sequences as well as alterations and substitutions are ambiguous, unclear and ill-defined.

B) Claims 10 is indefinite in the recitation of "Campath-1 antibody" because its characteristics are not known. The use of "Campath-1" antibody as the sole means of identifying the claimed antibody and hybridoma renders the claim indefinite because this is merely a laboratory designation which does not clearly define the claimed product, since different laboratories may use the same laboratory designation s to define completely distinct antibodies or cell lines.

C) Claim 10 contains the trademark or trade name "CAMPATH-1". Where a trademark or trade name is used in a claims as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 USC 112, second paragraph, See Ex parte Simpson, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark or the trade name "CAMPATH-1" is used to identify or describe a an anti-CD52 antibody, and accordingly, the identification or the description is indefinite. The relationship between a trademark or tradename and the product it identifies may be uncertain and arbitrary. The formula or characteristics of the product may change from time to time and yet it may continue to be sold under the same trademark or tradename.

D) Claims 1-17 and 22: The instant claims are indefinite in that the recitation of "the antibody molecule" in line 4 of claim 1 lack antecedent basis.

E) Claims 2, 8, 13 and 22 are indefinite in the recitation of "the same or substantially the same amino acid sequence" and "substantially human origin other than the CDRs" because it is ambiguous and unclear what is meant by "substantially". These phrases are relative in nature which renders the claims indefinite. These phrases are not defined by the claims and the specification does not provide a standard for ascertaining the requisite degree and, in turn, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention. Given that all species use the same genetic code; an amino acid or amino acid sequence amino acid sequence is not necessarily human in nature.

F) Claims 1-17 and 22 are indefinite in the recitation of "inducing immunological tolerance" because tolerance is an immunological phenomenon consisting of acquired incapacity of an individual to a particular antigen, which is a complex and multifaced phenomenon. Immunological tolerance can be induced in adult individuals by giving weak protein antigens either in repeated small doses or in large amounts (e.g. low-zone / high-zone tolerance). Given the various meanings of the term tolerance (complete lack of response to some level of response); given that tolerance is complex phenomenon and not necessarily achieved in humans; given that tolerance is a result of various methods and not necessarily a feature of a product per se; the metes and bounds of intended use or function of the claimed products for inducing tolerance is unclear and ill-defined.

G) The applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter. See MPEP 714.02 and 2163.06

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CAR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

16. For examination purposes with respect to prior art issues and given the absence of structural limitations in the claims as well as the issues set forth above in the rejections under 35 USC 112, first and second, paragraphs; the claimed modified antibodies are encompassed by modified antibodies that have reduced affinity for their respective cell surface antigen specificity than its parent molecule.

The intended uses of the claimed products either as a therapeutic antibody or antibodies that induce immunological tolerance do not carry patentable weight per se. A composition is a composition irrespective of what its intended

The recitation of a process limitation in the instant claims is not seen as further limiting the claimed product, as it is presumed that equivalent products can be obtained by multiple routes. The burden is on the applicant to establish a patentable distinction between the claimed and referenced antibodies. The patentability of a product does not depend on its method of production. In re Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985) See MPEP 2113

17. Claims 1-17 and 22 are rejected under 35 U.S.C. § 102(e) as being anticipated by Waldmann et al. (U.S. Patent No. 5,846,534) (see entire document). Waldmann et al. teach CAMPATH-1-specific antibodies and fragments thereof as well reshaping variable domains resulting in changes in antibody body (see Examples). In addition, Waldmann et al. Teach recycling the hypervariable regions on different human framework regions should change the idiotype (see column 4, paragraph 2). Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced antibodies and fragments thereof. It would have inherent in selecting and screening for humanized antibodies that the resultant antibodies would have had differing affinities, including those less than the native antibody. Also, fragments would have less affinity than the native molecule.

18. Claims 1-17 and 22 are rejected under 35 U.S.C. § 102(e) as being anticipated by Crowe et al. (U.S. Patent No. 5,858,725) (see entire document). Crowe et al. teach preparation of humanized antibodies and fragments using recombinant strategies including the CAMPATH-1-specific antibody (e.g. Example 1). Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced antibodies and fragments thereof. It would have inherent in selecting and screening for humanized antibodies that the resultant antibodies would have had differing affinities, including those less than the native antibody. Also, fragments would have less affinity than the native molecule.

19. Claims 1-17 and 22 are rejected under 35 U.S.C. § 102(e) as being anticipated by Carter et al. (U.S. Patent No. 6,054,297) (see entire document). Carter et al. teach preparation of humanized antibodies and fragments using recombinant strategies including the CAMPATH-1-specific antibody (column 2, paragraph 4). Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced antibodies and fragments thereof. It would have inherent in selecting and screening for humanized antibodies that the resultant antibodies would have had differing affinities, including those less than the native antibody. Also, fragments would have less affinity than the native molecule.

20. Claims 1-9, 13-17 and 22 are rejected under 35 U.S.C. § 102(b) as being anticipated by Isaacs et al. (Therapeutic Immunology 1: 303 -312, 1994; 1449) (see entire document, including the Abstract). Isaacs et al. teaching non-cell binding variants of therapeutic antibodies could be usefully exploited to generate therapeutic unresponsiveness to clinically useful antibodies. Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced antibodies and fragments thereof.

21. Claims 1-17 and 22 are rejected under 35 U.S.C. § 103(a) as being unpatentable over by Waldmann et al. (U.S. Patent No. 5,846,534) OR Crowe et al. (U.S. Patent No. 5,858,725) OR Carter et al. (U.S. Patent No. 6,054,297) in view of Isaacs et al. (Therapeutic Immunology 1: 303 -312, 1994; 1449).

Waldmann et al., Crowe et al. and Carter et al. are all taught above and differ from the instant claims by not teaching non-cell binding variants of therapeutic antibodies could be usefully exploited to generate therapeutic unresponsiveness to clinically useful antibodies.

Isaacs et al. teaching non-cell binding variants of therapeutic antibodies could be usefully exploited to generate therapeutic unresponsiveness to clinically useful antibodies (see entire document, including the Abstract).

One of ordinary skill in the art at the time the invention was made would have been motivated to select non-cell binding antibody variants, including fragments, of therapeutic antibodies, including the CAMPATH-1 antibody, to generate therapeutic unresponsiveness to clinically useful antibodies by a variety of recombinant means available to the ordinary artisan at the time the invention was made, as evidenced by Waldmann et al, Crowe et al. and Carter et al. Therefore the claimed limitations encompassing substitutions and alterations in sequences as well as reduced affinity would have been expected properties of selecting for non-cell binding variants of therapeutic antibodies at the time the invention was made. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

22. No claim is allowed.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Phillip Gambel, PhD.
Primary Examiner
Technology Center 1600
September 5, 2000